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REVIEW ARTICLE

Medications for chronic pain practical review

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Abstract

This review is confined to the drug management of chronic pain, and is specifically adapted to the resource-poor environment and the HIV pandemic of sub-Saharan Africa. A brief classification of chronic pain is followed by a discussion of the different classes of medications in use, including those used in migraine. An approach to the rational drug management of neuropathic pain is presented. In conclusion some general principles for prescribing in this setting are derived.

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Introduction

The patient with intractable chronic pain (such as low back pain, headache, 'rheumatism' or burning feet) is well known to all primary care physicians, and to most specialists. He or she is the 'heartsink patient', who will take up precious time, yet again going through the same symptoms which never improve, and which feel like a catalogue of the physician's failures. "Yes, you tried that it never did a thing," is a recurring theme, evoking profound apprehension and anxiety in the doctor when he sees the familiar face in his waiting room. Effective treatment, and above all a consistent plan of action in dealing with such unfortunate people is much needed.

Chronic pain has been shown to affect at least one adult in five in Europe,[1] and serious and time-consuming. More than cancer or heart disease, painful conditions including osteoarthritis and back pain have the largest negative impact on quality of life of all chronic conditions for people living in the community.[2]

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Experts in pain management, and standard textbooks on the subject, emphasise the multidisciplinary nature of the field. They point out that many different modalities of treatment are available, including psychological support, physical therapy, relaxation therapy, surgical interventions, nerve blocks, occupational interventions and counselling services. In sophisticated centres such multifaceted teams do often improve their patients' quality of life after years of suffering. However, for the majority of patients access to dedicated pain clinics is unrealistic, and the primary care physician needs to be in straight forward review of commonly used medications is presented here, without reference to the many other available modalities.

Pain Subtypes.

At this juncture, it will be helpful to review the classification of pain. Practically, it is important to decide whether a particular patient's pain is nociceptive (from a noxious stimulus), neuropathic (because of injury in the nervous system) or psychogenic (without structural or other organic damage). Examples of 'simple' nociceptive pain are post operative pain, mechanical low back pain, sports injuries or arthritis. Examples of neuropathic pain include post herpetic neuralgia, radicular pain from root compression because of a prolapsed intervertebral disc, painful neuropathy and trigeminal neuralgia. Psychogenic pain is often atypical, bizarre ("my scalp feels like it is bubbling") and non-anatomical in distribution. It may accompany or complicate other pain types.

'Simple' Analgesics.

Paracetamol and prostaglandin inhibitors (including cyclo-oxygenase 2 [COX-2] inhibitors) are often referred to as simple analgesics, and include many commonly used anti-infammatories, such as aspirin, ibuprofen, mefenamic acid, indomethacin, piroxicam and diclofenac. They all exhibit effectiveness in nociceptive pain, but do have different side effects and toxicities.

Aspirin is unsuitable under the age of 12 years because of the risk of Reye's syndrome, but is excellent for pain of noxious types, especially inflammatory, in adults. Chronic use in high doses is limited by gastric irritation and the risk of interstitial nephritis. It may be a powerful adjunct in treating pain from bony and other metastases. It is at least as effective as other anti-inflammatories such as diclofenac, ibuprofen, piroxicam and others.

Paracetamol has little anti-inflammatory activity, but is probably justifiably the most widely used analgesic medication it has a good safety profile, can be used as an antipyretic in febrile illnesses and is not an irritant to the gastric mucosa. It should be noted that with regular high doses (more than six tablets a day) analgesic rebound headache has been reported with paracetamol.

COX-2 inhibitors enjoyed tremendous popularity for several years, because of the much reduced incidence of gastric mucosal erosions and irritation even when gastroprotective strategies such as the use of proton pump inhibitors are used with NSAIDs.[3] However, reports of cardiac rhythm disturbances leading to unexpected deaths have led to a sharp downturn in their use. At present their routine use for chronic pain is controversial, although it has been only two agents in this class which were implicated.

Principle.

These drugs are the first choice and initial treatment for the vast majority of pain syndromes. The most sensible approach to the use of simple analgesics is to be very familiar with one or two common agents and to use them consistently, being aware of all (even rare) adverse effects and interactions as well as contra-indications. The vast array of duplicates available is confusing, especially when patients exhibit strong brand loyalties and display placebo effect. ("Panado works so much better than paracetamol" identical composition). A sympathetic but rational attitude is worth maintaining, not being needlessly rigid but at the same time not pandering to requests which may have harmful consequences ("if I re-prescribe her favourite medication I will at least get her off my back for the next month" must be a tempting thought for many practitioners).

Compound Analgesics.

Combinations of simple analgesics with codeine are popular for use in moderately severe pain, and certainly have a place in acute pain, especially nociceptive type. The use of compound medications in CHRONIC pain is discouraged, because of the frequency of drug interactions and adverse effects. In particular, paracetamol and codeine preparations with or without caffeine and an antihistamine or a muscle relaxant are likely to lead to unwanted rebound effects, sedation (resulting in patients taking analgesics for night sedation!) and impaired cognition.

Table I: Compound analgesics.

Combination	Brand names
Paracetamol and codeine	*Panadeine, Cocodamol, Betapyn, Pynstop*
Paracetamol, codeine, + 'muscle relaxant'	*Stopayne, Goldgesic (meprobamate)*
Paracetamol and 'muscle relaxant' (antihistamine)	*Besemax, Norflex Co (ophenadrine)*
Aspirin and codeine	*Codis*

Principle.
The same general principle as for simple analgesics applies know one or two drugs well, and especially be aware of drug interactions and adverse effects. In addition: at each time of re-prescription ask yourself what the justification for continuing a compound analgesic drug long term is at this time. Tolerance and rebound pain as well as dependence are all commoner with compound analgesics preparations.

Opioids.
Medications containing a naturally derived or synnthetic opiod derivative, are the mainstay of medical management of chronic severe somatic pain, and are widely used in palliative care, but also for non-malignant pain.[4] Despite their widespread use and availability, it is surprising how frequently effective pain relief is not achieved. This usually relates to concerns by the prescriber that large doses may cause respiratory depression, dependence or other undesirable effects. Very often the role of hospice to ensure that an adequate does is prescribed, and that any adverse effects that do occur are appropriately managed. The use of oral and other opioids in palliative care has become a specialised field and it is well worth soliciting expert assistance in patient care.

Because of their efficacy, it is tempting to use opioids for all types of severe pain, including neuropathic and psychogenic pain. In these categories the adverse effects may often outweigh the advantages, and especially for neurogenic pain opioids should be reserved as a last resort.

Table II: Opioid analgesics.

Drug	Route	Dose	Comment
Codeine	oral	30 -90 mg qid	Under utilised for moderately severe acute pain. Usual adverse effects are constipation, nausea.
Dihydrocodeine (DHC)	oral	30mg 4-6 hourly	More effective than codeine. Often not available.
Dextropopoxyphene (Doxyol)	oral	1-2 tabs 3 hourly	Equivalent to DHC; sedation, dizziness, confusion common.
Morphine	oral, IV, IM	Very wide range, Usually start at 10-20mg 4 hourly oral	Constipation, nausea invariable, often needs to be given with an anti-emetic and stool softener.
Pethidine	IV/IM, (oral)	50-100mg 4 hourly	No advantage over morphine.
Tramadol	oral	50-100mg 4-6 hourly	Equivalent to DHC.
Fentanyl	IV/IM/transdermal patch	60mg/day of oral morphine = 1mcg/hr of fentanyl patch	Equivalent to morphine, expensive. Patch avoids some GI side effects, injections.

Different preparations, as usual, have distinct profiles of adverse effects:

- Codeine (and dihydrocodeine) are favoured by neurosurgeons and others dealing with head injuries because they are more effective than simple analgesics and do not generally lead to impaired cognition and sedation (which could be confused with symptoms of complications of the injury). In this setting both drugs are very effective if inevitable constipation and frequent nausea are addressed. In the chronic setting their effectiveness often declines rapidly, leading to tolerance and rebound pain.
- Dextro-propoxyphene is often used for severe chronic pain not responsive to compound analgesics, such as mechanical back pain or headache, but its use may lead to cognitive impairment (confusion or dizziness, even hallucinations), moderate pain because of the

theoretical advantage that a combined mu receptor agonist and antagonist has, in being less susceptible to the development of tolerance.

- Morphine in oral form, either tablets (including sustained release preparations) or as a syrup, is used in chronic nociceptive pain when other medications and modalities have not been effective. Its use is governed by adherence to the principles of upward titration and addressing adverse effects. Regular and frequent doses to prevent pain are often better than "as required" dosing.
- Transdermal preparations (fantanyl and buprenorphine) in the form of patches can gastro-intestinal symptoms, but are expensive.[5,6]

Principle.

In chronic severe somatic pain opioid drugs are the mainstay of treatment, but their use is associated with significant adverse effects which must be anticipated and managed. Too often insufficient doses or too long dosing intervals render treatment inadequate titration to pain relief is the key. This may be achieved by monitored dose increases until therapeutic effect is reached, treating adverse effects as they arise or sometimes pre-emptively (e.g. constipation, nausea).

Neuropathic Pain.

When pain has burning or stabbing ('lancinating') qualities, it may be caused by damaged neural structures: peripheral nerve fibres, roots, dorsal ganglion cells, or central pathways (spinal, brainstem, thalamic or cortical). The distribution and accompanying sysmptoms often help clarify the location of the source.[7] A significant number of patients with hemisensory distribution of pain and other subjective phenomena (paraesthesia, feeling hot or cold) have no organic pathology and may be somatising, or 'amplifying' (e.g. chest and truncal pain with carpal tunnel syndrome) other symptoms. Pain may accompany acute injury (as with a foraminal intervertebral disc prolapse) or arise much later, when healing is already complete (as in post herpetic neuralgia).

The two classes of drugs conventionally used in this situation if simple analgesics are unhelpful are tricyclic anticholinergics (amitriptyline, imipramine, nortriptyline) and anticonvulsants (carbamazepine, phenytoin, gabapentin, lamotrigine).[8] Both of these groups were originally used for other indications and have considerable adverse effects, often dose-limiting. The newer anticonvulsants, such as gabapentin and more recently pregabilin and lamotrigine, have fewer adverse effects and thus higher doses are tolerated. They have become a first choice for clinicians treating neuropathic pain where they are available.[9]

In general, the tricyclic drugs and derivatives tend to be more effective for diffuse burning pain which is poorly localised (as in "burning feet" of painful peripheral neuropathy), whilst anticonvulsants are more useful in the very localised sharp "lancinating" pain with shooting qualities in a specific radiation of particular nerve or root irritation/compression (for example in trigeminal neuralgia). In addition central pain syndromes, for example after a thalamic stroke, may also respond o anticonvulsants.

After peripheral or plexus injuries intractable pain with skin and skeletal changes (complex regional pain syndrome) may result. Treatment with medications is often frustrating, and a combined approach with regional and central blocks and consideration of neurosurgical procedures (such as dorsal root entry zone stimulation) should be undertaken.[10]

Table III:

Drug	Route	Dose	Drug class	Comment
Amitriptyline	Oral	12.5 mg nocte - 150mg nocte	tricyclic	Slow upward titration, expect transient drowsiness.
Imipramine (Nortiptyline)	Oral	25 mg daily -	tricyclic	Less sedating, less effective.
Dothiepin	Oral	25 mg nocte -	tricyclic	Similar to imipramine.
Duloxetine	Oral	30 - 60 mg twice daily	new tricyclic derivative	New combined anticholinergic, and anti-adrenergic, used in diabetic neuropathy.
Carbamazepine	Oral	100 mg nocte - 400 mg tds	anticonvulsant	Drowsiness, ataxia often limit dose.
Phenytoin	Oral	100 mg nocte - 200 mg bd	anticonvulsant	More side effects than carbamazepine, sometimes useful in combination.
Gabapentin (Neurontin)	Oral	100 mg nocte - 900 mg tds	anticonvulsant	As effective as carbamazepine, higher doses tolerated, first choice when Available.
Pregabalin (Lyrica)	Oral	150-600 mg daily (50-200 200 mg tds	anticonvulsant	Licensed in USA for diabetic neuropathic pain, less sedating.
Lamotrigine	Oral	50 mg daily to 200 mg bd	anticonvulsant	Very little sedation, effective.
Lignocaine Patch	Topical		local anaesthetic	Limited use in post herpetic pain.

Principle.
Older drugs generally have more side effects but are more available and cheaper. Use what is available and abandon older drugs when side effects (especially sedation and ataxia, but not forgetting to ask about hallucinations, reduced libido and incontinence) are unacceptable. Most medications in these classes should be started at low doses and increased very slowly, over weeks. An example would be amitryptiline for painful neuropathy: 10 or 12.5mg at night for one week, 25mg at night for one week, 50mg at night for one week. If there is insufficient pain relief on 50mg: give 75mg for two weeks, and 100mg for two weeks. If un acceptable side effects stay on lower dose for longer before increasing.

Migraine: A Special Case.
Many people with chronic pain have headache, which may be quite intractable and present for years. A large proportion of these have frequent or chronic migraine,[11] and because medications for migraine prophylaxis and treatment are specific to the condition, a brief discussion follows.

1. As always, the most accurate and complete diagnosis possible is the first step. Many headache sufferers have mixed headaches, with chronic tension type and analgesic rebound components as well as migrainous elements.
2. Migraine management includes avoiding or minimising precipitants, abortive treatment for individual headaches, and prophylaxis. Abortive treatment may consist of simple analgesics including anti-inflammatories, ergotamine derivatives or triptans, often with and anti-emetic. Often a stepwise progression is advocated: if a simpler medication is effective the next step is necessary.
3. Prophylactic treatment is advised when headaches are very frequent and/or disabling this does vary with individual sufferers.[12] Two or more disabling migraines a month (sufficient to prevent sufferers from attending work or school) is a reasonable rule of thumb in intermittent migraine, but in chronic/transformed migraine individual headaches are usually less severe and indications are less clear-cut.

Principle.
Once the diagnosis and requirement for prophylaxis are clear, treatment for migraine should be aggressive, with clear monitoring (by the use of headache diaries) and treatment goals. There is usually a trade-off between therapeutic and adverse effects. This should be negotiated with the patient, taking into account the tendency form many cognitive and drowsiness-related side effects to attenuate over time.

Table IV:

Drug	Dose	Drug Class	Effectiveness	Comment
Propranolol*	20 - 160mg tds (80-720mg daily of long acting prep.)	Beta blocker	++++	Very effective. Avoid in asthma, peripheral arterial disease. May cause depression, insomnia.
Amitriptyline	25 - 100mg nocte	Tricyclic anticholinergic	+++	Effective, especially if tension type headache also present. Sedating. Cognitive side effects in elderly (Avoid over 65).
Valproate*	200-500mg tds	Anticonvulsant	+++	Effective, sedating. May cause weight gain, hair loss.
Flunnarizine (Sibelium)	80 mg daily	Calcium channel antagonist	++	No randomised control trial evidence, but few side effects.
Topiramate* [13]	25-100mg bd	Novel anticonvulsant	++++	Effective, but difficult to use with + side effects.
Levetiracetam	500-1000mg	Novel	++++	Preliminary evidence good, Expensive.

Many other medications have been used, for example other beta blockers, other tricyclics and herbal remedies. Solid evidence for efficacy is available for those marked*.

Conclusion

When confronted by a patient with chronic pain, and planning medications, there is indubitable merit in having a clear approach. It is useful for the prescriber to ask himself or herself some questions:

1. What am I treating (What is the diagnosis, what type of pain is this?).
2. Is there appropriate non-pharmacological treatment that should be considered? (including psychological, physical, nerve blocks, surgery)?
3. What class of medications is most suitable?
4. Where is the patient in terms of what (appropriate or inappropriate) medications and other treatments he has previously received?
5. Which adverse effects can be anticipated for the planned treatment?
6. What is the limit for adverse effects for this patient and this treatment?
7. How will I measure effectiveness and adverse effects?

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